**Citation:**

Salas-Salvado J, Garcia-Arellano A, Estruch R, Marquez-Sandoval F, Corella D, Fiol M, Gómez-Gracia E, Viñoles E, Arós F, Herrera C, Lahoz C, Lapetra J, Perona JS, Muñoz-Aguado D, Martínez-González MA, Ros E; PREDIMED Investigators. Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease.*Eur J Clin Nutr*. May 2008; 62 (5): 651-659.

**PubMed ID:** 17440519

**Study Design:**

Prospective cohort study

**Class:**

B - Click here for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To evaluate associations between components of the Mediterranean diet and circulating markers of inflammation in a large cohort of asymptomatic subjects at high risk for cardiovascular disease.

**Inclusion Criteria:**

Community-dwelling people (age 55-80 years of age for men; 60-80 years of age for women) who fulfilled at least one of two criteria: Type 2 diabetes and three or more CHD risk factors

- The diabetes criterion was defined as a previous diagnosis of non-insulin-dependent diabetes, or fasting plasma glucose concentration greater than or equal to 120 mg/dL observed on two consecutive occasions
- The CHD risk-factor criteria included current smoking, hypertension (blood pressure >140/90mmHg, or treatment with anti-hypertensive drugs), low-density lipoprotein (LDL) cholesterol greater than or equal to 160mg/dL (or treatment with hypolipidaemic drugs), low high-density lipoprotein (HDL) cholesterol ≤40mg/dL, body mass index (BMI) ≥25kg/$m^2$, or family history of premature CHD.

**Exclusion Criteria:**

- Previous history of cardiovascular disease
- Any severe chronic illness
- Drug or alcohol abuse
- History of allergy or intolerance to olive oil or nuts.

**Description of Study Protocol:**

**Recruitment**

- The primary-care physicians based their selection of participants on a review of the subjects's clinical record and a screening visit
- A list of candidates was obtained from computer-based records of patients regularly attending each of the participating centers
- Potentially eligible candidates were contacted by telephone and invited to attend a screening visit.

**Design**

Cohort, cross-sectional.

**Dietary Intake/Dietary Assessment Methodology**

- Energy and nutrient intake were calculated from Spanish food composition tables
- The baseline examination included the administration of a 14-item questionnaire indicating the degree of adherence to the traditional Mediterranean diet that is an extension of a previously validated questionnaire
    - Values of zero or one were assigned to each of 14 dietary components
    - Subjects whose consumption of the 'beneficial' foods (olive oil, vegetables, legumes, fruits, nuts, fish and seafood, white meats instead of red meats, home-made sauces, red wine) was below a pre-specified value were assigned a value of zero and those above this pre-specified value were assigned a value of one
    - Conversely, subjects whose consumption of 'detrimental' foods (red meats, fat-rich dairy products, commercial pastries and snacks, artificially sweetened beverages) was above a pre-specified value were assigned a value of zero and a value of one if the values were below the pre-specified cutoff point. The cutoff point of each specified item was established in accordance with the results of a case control study that evaluated the risk of first non-fatal myocardial infarction.

**Blinding Used**

Not described.

**Statistical Analysis**

- All statistical analyses were performed with the SPSS package, version 12.0
- All tests were two-tailed and P-values <0.05 were considered statistically significant
- When appropriate, values were transformed to their natural logarithm before statistical analyses
- Participants were categorized by tertiles of food-group consumption. Means and standard deviations (SD) were calculated for each inflammatory marker within each tertile of food groups or selected food items. The same procedures were performed on the score indicating the level of participant's adherence to the Mediterranean-type diet
- Values are presented as unadjusted means and SD and 95% confidence interval (CI)
- Values were adjusted for potential confounding variables using ordinary least-squares regression models
- Log-transformed values of inflammation markers were used as the dependent variables and

food consumption as the independent variables (using two dummy variables for the second and third tertile of consumption of each food group or food item)
- Data in the models were controlled for age (continuous), gender, BMI (continuous), smoking (three categories) and diabetes (yes/no)
- Linear trends were tested using the median of each tertiles as a continuous variable after adjusting for the confounding variables mentioned above
- Further analyses were performed controlling for the use of specific drugs (statins, non-steroidal anti-inflammatory agents and aspirin).

**Data Collection Summary:**

**Timing of Measurements**

Blood samples were taken after fasting.

**Associated Variables**

- Cereal, fruits, vegetable, oil, alcohol consumption (grams per day) determined from semi-quantitative food frequency questionnaire (FFQ)
- C-reactive protein (CRP), interleukin-6 (IL-6), intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)
- Serum concentrations of high-sensitivity CRP were measured by immunonephelometry and those of IL-6, ICAM-1 and VCAM-1 by enzyme-linked immunosorbent assay.

**Control Variables**

- Age
- Gender
- BMI
- Diabetes
- Smoking
- Use of statins
- Non-steroidal anti-inflammatory drugs
- Aspirin.

**Description of Actual Data Sample:**

- *Initial N:* 930
- *Attrition (final N):* 772 (339 men and 433 women)
- *Age:* Mean (SD) in years:
  - Men=67.6 (6.5)
  - Women=69.8 (6.2)
- *Ethnicity:* Not described
- *Other relevant demographics:* Not applicable
- *Anthropometrics:* BMI; mean (SD):
  - Men=29.0kg/$m^2$ (3.7)
  - Women=30.3kg/$m^2$(4.6)
- *Location:* Various cities in Spain.

**Summary of Results:**

- After adjusting for age, gender, BMI, diabetes, smoking, use of statins, non-steroidal anti-inflammatory drugs and aspirin, a higher consumption of fruits and cereals was associated with lower concentrations of IL-6 (P for trend 0.005; both)
- Subjects with the highest consumption of nuts and virgin olive oil showed the lowest concentrations of VCAM-1, ICAM-1, IL-6 and CRP; albeit only for ICAM-1 was this difference statistically significant in the case of nuts (for trend 0.003) and for VCAM-1 in the case of virgin olive oil (P for trend 0.02)
- Participants with higher adherence to the Mediterranean-type diet did not show significantly lower concentrations of inflammatory markers (P<0.1 for VCAM-1 and ICAM-1).

**Author Conclusion:**

The consumption of some typical Mediterranean foods (fruits, cereals, virgin olive oil and nuts) was associated with lower serum concentrations of inflammatory markers, especially those related to endothelial function in subjects with high cardiovascular risk living in a Mediterranean country.

***Reviewer Comments:***

- *Well-conducted study*
- *Related to Research Design and Implementation Rating Checklist:*
  - *5.3. Unclear. Blinding was not described in the methods section.*

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***Research Design and Implementation Criteria Checklist: Primary Research***

**Relevance Questions**

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|---|---|---|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | N/A |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about? | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice? | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies) | N/A |

**Validity Questions**

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|---|---|---|
| **1.** | **Was the research question clearly stated?** | Yes |

| | | |
|---|---|---|
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified? | Yes |
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated? | Yes |
| 1.3. | Were the target population and setting specified? | Yes |
| **2.** | **Was the selection of study subjects/patients free from bias?** | Yes |
| 2.1. | Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? | Yes |
| 2.2. | Were criteria applied equally to all study groups? | Yes |
| 2.3. | Were health, demographics, and other characteristics of subjects described? | Yes |
| 2.4. | Were the subjects/patients a representative sample of the relevant population? | Yes |
| **3.** | **Were study groups comparable?** | Yes |
| 3.1. | Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) | N/A |
| 3.2. | Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? | N/A |
| 3.3. | Were concurrent controls used? (Concurrent preferred over historical controls.) | N/A |
| 3.4. | If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? | Yes |
| 3.5. | If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) | N/A |
| 3.6. | If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")? | N/A |
| **4.** | **Was method of handling withdrawals described?** | Yes |
| 4.1. | Were follow-up methods described and the same for all groups? | Yes |
| 4.2. | Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) | Yes |

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| 4.3. | Were all enrolled subjects/patients (in the original sample) accounted for? | Yes |
| 4.4. | Were reasons for withdrawals similar across groups? | Yes |
| 4.5. | If diagnostic test, was decision to perform reference test not dependent on results of test under study? | N/A |
| **5.** | **Was blinding used to prevent introduction of bias?** | Yes |
| 5.1. | In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? | N/A |
| 5.2. | Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) | Yes |
| 5.3. | In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? | ??? |
| 5.4. | In case control study, was case definition explicit and case ascertainment not influenced by exposure status? | N/A |
| 5.5. | In diagnostic study, were test results blinded to patient history and other test results? | N/A |
| **6.** | **Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?** | N/A |
| 6.1. | In RCT or other intervention trial, were protocols described for all regimens studied? | N/A |
| 6.2. | In observational study, were interventions, study settings, and clinicians/provider described? | N/A |
| 6.3. | Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? | N/A |
| 6.4. | Was the amount of exposure and, if relevant, subject/patient compliance measured? | N/A |
| 6.5. | Were co-interventions (e.g., ancillary treatments, other therapies) described? | N/A |
| 6.6. | Were extra or unplanned treatments described? | N/A |
| 6.7. | Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? | N/A |
| 6.8. | In diagnostic study, were details of test administration and replication sufficient? | N/A |
| **7.** | **Were outcomes clearly defined and the measurements valid and reliable?** | Yes |
| 7.1. | Were primary and secondary endpoints described and relevant to the question? | Yes |
| 7.2. | Were nutrition measures appropriate to question and outcomes of concern? | Yes |

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| 7.3. | Was the period of follow-up long enough for important outcome(s) to occur? | N/A |
| 7.4. | Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? | Yes |
| 7.5. | Was the measurement of effect at an appropriate level of precision? | Yes |
| 7.6. | Were other factors accounted for (measured) that could affect outcomes? | Yes |
| 7.7. | Were the measurements conducted consistently across groups? | Yes |
| **8.** | **Was the statistical analysis appropriate for the study design and type of outcome indicators?** | Yes |
| 8.1. | Were statistical analyses adequately described and the results reported appropriately? | Yes |
| 8.2. | Were correct statistical tests used and assumptions of test not violated? | Yes |
| 8.3. | Were statistics reported with levels of significance and/or confidence intervals? | Yes |
| 8.4. | Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? | N/A |
| 8.5. | Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? | Yes |
| 8.6. | Was clinical significance as well as statistical significance reported? | Yes |
| 8.7. | If negative findings, was a power calculation reported to address type 2 error? | N/A |
| **9.** | **Are conclusions supported by results with biases and limitations taken into consideration?** | Yes |
| 9.1. | Is there a discussion of findings? | Yes |
| 9.2. | Are biases and study limitations identified and discussed? | Yes |
| **10.** | **Is bias due to study's funding or sponsorship unlikely?** | Yes |
| 10.1. | Were sources of funding and investigators' affiliations described? | Yes |
| 10.2. | Was the study free from apparent conflict of interest? | Yes |